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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,059	WILDE ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *November 6, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's amendment and remarks submitted November 6, 2006 wherein claims 1, 9, 16, and 19 are amended and claims 20-28 are cancelled. This application claims benefit of provisional application 60/398334, filed July 24, 2002.

Claims 1-19 are pending in this application.

Claims 1-19 as amended are examined on the merits herein.

Applicant's argument, filed November 6, 2006, with respect to the rejection of instant claim 19 under 35 USC 102(b) as being anticipated by Moss et al., (of record in the previous office action) has been fully considered and found to be persuasive to remove the rejection as Applicant has pointed out that the cell lines used by Moss et al. are leukemia cell lines and thus outside of the scope of instant claim 19. Thus the rejection is withdrawn.

The requirement for election of species, made April 14, 2006, is withdrawn. All claimed species are examined in the merits herein.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 9-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims include structural elements defined as substituted or unsubstituted alkyl, aryl, heteroaryl, cycloalkyl, heterocyclo, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, or arylcarbonyl. It is not defined what substituents these groups may or may not be substituted with. P. 9, line 21 – p. 10, lines 7 recites a number of suggested groups which are included within the definition of substituents, but this definition is not limiting and does not indicate which groups are not suitable as substituents. Therefore the claims are indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 9-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising administering the species recited in claim 7, does not reasonably provide enablement for a method comprising administering any compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic method comprising administering a compound to a patient.

The state of the prior art: Clitocine, a compound of the formula recited in claim 7, is known in the prior art to have cytotoxic properties toward cancer cells. Furthermore, methods of suppressing nonsense mutations with aminoglycosides or with artificial tRNAs are known in the art and have been used to correct nonsense mutations such as those giving rise to muscular dystrophy.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The structure of formula I comprises a large number of nucleoside analogs having various base moieties. The base moiety comprises a nitrogen substituted with either one or two substituted or unsubstituted alkyl, aryl, heteroaryl, cycloalkyl, heterocyclo, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, or arylcarbonyl. As no limit is given as to what these groups may be substituted with, practically any exocyclic amine is included within the limitations of this claim. Because the nucleotide moiety of a nucleoside is very important for determining its interactions with DNA and RNA, as well as with ribosomes

and proteins that interact with nucleosides, compounds of formula I are expected to vary widely as to their biological activities. It is therefore not possible to predict the biological activity of all compounds of this class based on the behavior of one specific embodiment such as clitocine.

It is also noted that nucleosides and nucleoside analogues are already known which possess biological activities other than nonsense suppression. For example, AZT is known as an antiviral agent while fluorouracil is known as a cytotoxic agent and N4-aminocytidine is known to be a mutagen. Therefore the biological function of the claimed compounds in expected to be highly unpredictable.

The Breadth of the claims: As mentioned above, the claimed invention is extremely broad, comprising methods of administering more or less any exocyclic nucleoside to a patient.

The amount of direction or guidance presented: Applicant's specification discloses a number of exocyclic nitropyrimidine analogs which are said to be nonsense suppressors. These compounds are not representative of the full range of chemical diversity present in the claimed invention as described above.

The presence or absence of working examples: Clitocine is shown to suppress nonsense mutations and inhibit cancer growth *in vivo*. No working examples are provided for other nucleosides besides clitocine.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as nonsense suppression. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of nonsense suppressing nucleosides beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular nucleoside is useful as a nonsense suppressor. For most nucleosides, it is unknown whether they are or are not useful as nonsense suppressors. Gathering this data for every compound falling within the claimed structural limitations would involve *in vitro* screening of an enormous diversity of chemical compounds for nonsense suppression activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential nucleoside nonsense suppressors, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every

possible nonsense suppressor, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of nucleosides claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all compounds of formula I.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 9-11, and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanghvi et al. (Reference included with PTO-892) Sanghvi et al. discloses the compounds 4-amino-(β-D-ribofuranosylamino)pyrimido[5,4-d]pyrimidine (ARPP, **8**) and 4-methoxy-(β-D-ribofuranosylamino)pyrimido[5,4-d]pyrimidine (MRPP, **14**). (p. 631, Scheme II at top of page) Both of these compounds fall within the limits of generic structure (I) in instant claim 1. They are both revealed to possess antitumor

properties, and thus to inhibit the growth of tumors. (p. 633, right column, last paragraph) Sanghvi et al. does not explicitly disclose a method of treating a tumor responsive to modulation of premature translation termination by administering either of these compounds to a patient.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer either ARPP or MRPP to a patient suffering from a tumor that is caused by premature translation termination in order to treat the tumor and inhibit its growth, and to administer the compound as part of an intravenous pharmaceutical composition further comprising a pharmaceutically acceptable carrier such as sterile water or saline. One of ordinary skill in the art would have been motivated to practice the invention in this manner because ARPP, MRPP and their anomers are already revealed by Sanghvi et al. to be useful for treating tumors *in vivo*. One of ordinary skill in the art would reasonably have expected success because these compounds are broadly known to be useful for treating tumors and because formulating and administering a known compound by a routine method such as intravenous administration is well within the ordinary, conventional, and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

The following rejections made in the previous office action are maintained:

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of specific p53-associated tumors such as the CAOV-3 cell line demonstrated in the specification by the administration of the claimed compounds, does not reasonably provide enablement for treatment of every type of cancer in existence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method for treating cancer by the administration of a nucleoside analogue which is capable of restoring function to genes disrupted by nonsense mutations. It is claimed that the compound restores function of tumor suppressor genes such as p53, thus inhibiting the growth of the cancer.

The state of the prior art: The skilled artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen. No single chemotherapeutic drug is useful for the treatment of every case of cancer. Indeed, some types of cancer to not respond well to any known chemotherapeutic drugs. According to the Merck Manual of Diagnosis and Therapy (Reference included with PTO-892), Hepatocellular carcinomas and renal cell carcinomas are not generally improved by chemotherapy. Acute lymphoblastic leukemia, on the other hand, responds well to a number of drugs, including vincristine, anthracyclines, and aspariginases, while acute mylogenous leukemia, on the other hand, responds to fewer drugs and is usually treated with cytarabine in combination with daunorubicin or idarubicin. Breast cancer, on the other hand, is best treated with surgery and/or radiation, but the prognosis can be improved by the addition of adjuvant chemotherapy.

The relative skill of those in the art: The level of skill in the art is high.

The predictability or unpredictability of the art: As mentioned above, no single treatment is effective for all cancers. Different cancers vary widely in their response to different chemotherapy regimens. According to the Oxford Textbook of Oncology, (Reference cited in PTO-892) "The important criteria for the tumor include its sensitivity to cytostatic drugs, its clinical stage and its mass, the presence of measurable lesions or biochemical markers, and, finally, growth characteristics," as well as, "*In vitro* sensitivity tests have been disappointing. They predict well for resistance but are of little use for sensitivity," (p. 451, right column, second paragraph) and, "For many types

of cancer the potential benefit of chemotherapy has not been demonstrated in well-designed clinical trials."

Based on the known teachings of the prior art such as that stated above, one skilled in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors, for example: gynecological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CAN, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by performing the necessary experimentation to develop an optimized protocol for treating said cancers. Further varieties of cancer which must also be treated successfully by the claimed invention are recited in instant claim 14.

The Breadth of the claims: Instant claims 1-13 are drawn to methods for treatment of any cancer with the claimed compounds, provided that said cancer is the result of a nonsense mutation in any gene. Instant claims 14-18 are drawn to methods for the treatment of a broad variety of recited cancers. Instant claim 19 is drawn to methods of inhibiting the growth of cancer cells *in vivo*.

The amount of direction or guidance presented: The probable mechanism by which the claimed therapeutic method exerts its effects is disclosed. Protocols are

provided for *in vitro* and *in vivo* inhibition of cancer cells. Clinically relevant properties such as the toxicity or therapeutic index, are not disclosed.

The presence or absence of working examples: The only *in vivo* working example provided in the specification is drawn to a treatment of a specific tumor cell line, CAOV-3, bearing a p53 nonsense mutation. *In vitro* examples are given for several p53 nonsense mutant cell lines: CAOV-3, NCI-H520, CALU-6, HCC1569, NCI-H774, and HCI-H1926. No examples are given for the treatment of cancers resulting from mutations in genes other than p53.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable art such as cancer chemotherapy. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the invention for all cancers beyond those disclosed in the specification, one skilled in the art would develop specific therapeutic regimens for each general type of cancer bearing a nonsense p53 mutation. One skilled in the art would have to perform further experimentation to develop therapeutic methods for treating cancers not associated with a single nonsense mutation, as these cancers are unlikely to be treatable through the mechanism disclosed in the instant specification. This would involve a process of optimizing and testing various regimens *in vivo* for each type of cancer being treated. This process would involve unpredictable experimentation which would constitute an undue experimental burden on the practitioner, with no guarantee that success is even possible for each case.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the unpredictability of the art and the breadth of the claims, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all types of cancer.

Response to argument: Applicant's amendment, submitted November 6, 2006, with respect to the above rejection, has been fully considered and not found persuasive to remove the rejection. The amendment narrows the scope of the claimed invention to include only those cancers in which the cancerous phenotype is caused by a nonsense mutation. Applicant argues that, with respect to the newly limited scope, the amended claims satisfy the requirements of *In re Bundy* by the disclosure of nonsense suppression activity coupled with the knowledge that this activity is useful for the treatment of cancer. However, in view of Applicant's disclosure, one of ordinary skill in the art would not be able to determine which cancers are and are not caused by nonsense mutations and are thus treatable by the claimed method. While there exist methods for locating a nonsense mutation in a specific known gene, such as p53, the cancerous phenotype can be the result of any one of a wide variety of genes, not all of which are known. Because cancer is the result of a spontaneous mutation rather than a transmissible infectious agent, different cases of cancer will be the result of different

mutations in different genes. Therefore the claimed invention is not enabled for methods of treating nonsense mutation associated cancers where the nonsense mutation is not located in a well characterized oncogene such as p53, and extending it to other types of cancers or other diseases would require an undue and highly unpredictable experimental burden. Thus the rejection is maintained.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating certain forms of cancer as discussed in the previous enablement rejection by administering the claimed compounds, does not reasonably provide enablement for prevention of cancer by administering the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the invention: The claimed invention is a therapeutic method for the prevention and treatment of cancer, involving the administration of a specific compound to a patient in need thereof. Because every living mammal is at risk of developing cancer, the patient population is not limited to those actually suffering from cancer. The invention is supposed to work by restoring full-length expression of tumor suppressor genes, particularly p53, which have been disrupted by nonsense mutations.

The state of the prior art: The state of the art for the treatment of nonsense mutations does not include any therapies directed to preventing nonsense mutation from occurring or preventing the occurrence of disease in those carrying them. Although various factors, such as exposure to radiation or certain chemicals, are known to increase or decrease a subject's risk of developing cancer, no methods for completely preventing the development of cancer by administration of a compound have been reported. Thus there is no precedent in the prior art for the prevention of this class of diseases, as opposed to treatment.

Aminoglycosides, the main class of nonsense suppressor agents known in the prior art, are known to be toxic as a result of their ability to disrupt normal protein synthesis and cause the misincorporation of amino acids into synthesized proteins. Long-term systemic administration of aminoglycosides is therefore not advisable. Because the claimed compounds is disclosed to possess a biological activity similar to that of aminoglycosides, it is expected to possess similar toxicity, and is in fact known in the art as an insecticide.

The relative skill of those in the art: The relative skill of those in the art is high, with a typical practitioner having obtained a PhD or equivalent advanced degree.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics,

chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer. This is especially the case when the drug in question, like most or all cancer drugs, possesses significant side effects which would be burdensome or life-threatening if therapy is continued indefinitely, and which outweigh the potential benefits of the therapy if the drug is administered to a healthy subject.

The Breadth of the claims: Claims 1-18 are drawn to a method of treating or preventing cancer. No limits are provided as to the scope of prevention claimed. Thus, to be fully enabling, the specification must disclose a therapeutic method capable of preventing anyone from ever being afflicted with cancer.

The amount of direction or guidance presented: All of the references to the potential of Clitocine as a cancer therapeutic disclosed or cited by the Applicant were published within the last twenty years, and none describe any experiments continued for a sufficient period of time to determine the long-term effectiveness of the disclosed therapy for preventing cancer over a subject's entire lifetime, rather than delaying the onset or reducing the symptoms of the disease. As the average human lifespan is between seventy and eighty years, the Applicant, or any other physician or researcher, could not have observed the long-term efficacy, or lack thereof, of the claimed therapeutic method. Rather than claiming an actual invention, the term "prevention" merely denotes a hope or prediction. The specification fails to address this concern or give any rationale as to why the disclosed treatment would be expected to be useful for prevention of disease. One practicing the claimed therapeutic method for prevention of

cancer would have no guidance from the specification, and would face an undue experimental burden in developing said method. Thus the long-term prevention of cancer is not supported or enabled by the specification.

The presence or absence of working examples: No working examples are presented demonstrating the success of this therapy for the prevention of cancer in the long term. Those working examples which are provided concern the short-term treatment of an existing cancer. It is also noted that the *in* vivo therapy disclosed in section 5.2.11 did not result in complete remission of the cancer being treated over the time period disclosed in figure 4/4 of the drawings.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as gene therapy. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for the treatment of disease is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy.

In particular, one skilled in the art would need to know whether the regular administration of clitocine over a period of decades would adversely affect the health of the subject, given the well-known toxic effects of other translation disrupting compounds

such as aminoglycosides, in order to determine the maximum safe dose for chronic use and to devise measures to be taken to reduce any side-effects.

Additionally, one skilled in the art, in order to practice the invention for prevention of cancer, would need to know whether the preventative effect remains potent over the long term. It is possible that long-term administration of clitocine will lead to the emergence of resistant tumors, as is the case for every other cancer drug observed so far.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or goats rather than the usual rodent models for cancer. The experiments would involve chronic administration of clitocine to a large population of healthy animals, with or without the additional administration of ionizing radiation or chemical carcinogens to put the animals at risk for the development of cancer. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering clitocine to a large population of dogs over a period of years, and monitoring the incidence of cancer in said population, is an undue amount of experimentation needed in order to practice the full range of the claimed invention.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of cancer.

Response to Argument: Applicant's arguments, submitted November 6, 2006, with respect to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that demonstrating safety and efficacy in humans is not a requirement for patentability. However, it is a requirement for patentability that one of ordinary skill in the art be able to make and use the invention in view of the disclosure. Furthermore, Applicant does not address the significant differences between treating a disorder, which is supported by the disclosure, and preventing the same disorder, which is included in the claimed invention. In the absence of a clear definition of prevention in Applicant's specification, the differences between treatment and prevention are interpreted as follows:

- In order to be considered successful, treatment need only bring about some measure of improvement in the patient's condition. Prevention, in order to be successful, must be completely successful at avoiding all symptoms of the disorder.

- Treatment need only function for a short duration, while prevention must either be permanent or must be continued indefinitely.
- Treatment may be administered after a patient has developed symptoms of a disorder, while prevention must be administered before the disorder manifests itself.
- Treatment may be effective in less than 100% of cases, while prevention must be completely, infallibly effective in every case.

Therefore, disclosure of a method of treating a disorder does not serve to enable a method of preventing the disorder. Rather, in order to enable prevention, Applicant must meet the additional burden of enablement associated with a preventative method. It should be noted that no medical treatment has ever met the standard required for "prevention" as defined above, and that one skilled in the art would thus have **no expectation whatsoever** that routine, predictable experimentation would succeed in accomplishing such a result. Such a result would be a miracle rather than a scientific discovery. Although certain treatments, such as vaccines, are referred to as "preventative" in the medical literature, the definition of prevention used with respect to such treatments is different than the definition used by the Office, as outlined above, and is therefore not relevant to the instant rejection. The routine practice of administering a therapy to a patient at risk for a disorder in order to reduce the likelihood or severity of the disorder, is considered to be included within the definition of the term "treatment," rather than "prevention."

Applicant further argues that the amount of experimentation needed to practice the claimed invention is merely routine, predictable experimentation. However, as discussed above, prevention is by its very nature a difficult and unusual result which is outside of the scope of the medical art. Therefore success is not only uncertain, but downright impossible, barring some unusual, unexpected discovery which would overturn the current state of the art.

Applicant also argues that the claimed therapy need not be continued indefinitely, and suggests that certain biological markers may be monitored in order to determine when therapy should be commenced and discontinued. This argument is not persuasive because Applicant's disclosure does not teach such markers or demonstrate that they would be sufficient to predict every case of nonsense mutation associated cancer, or that they would be able to discriminate between nonsense mutations and other sorts of mutations. Measuring the plasma level of a protein or mRNA only serves to monitor the expression level of one particular gene. Furthermore, because the claimed invention does not correct the underlying genetic defect but merely compensates for it by allowing a low level of expression of the gene product, it is not expected that a patient suffering from a somatic mutation would, as a result of treatment with this therapy, have the mutation reversed.

Finally, Applicant describes the rationale behind the claimed treatment and claims that it is reasonable to expect that the treatment could be used on a subject known to have a nonsense mutation, thus preventing the disease. Applicant appears to be confusing the terms "treating," and "preventing" as described above, as well as

confusing somatic and germ-line mutations. A somatic nonsense mutation, as opposed to an inherited germ-line mutation, is not present in the majority of a patient's cells and cannot be detected by screening a genetic sample from the patient unless the sample has been taken from a cell bearing the mutation. By the time that, for example, a nonsense mutation in an oncogene, is present in enough cells to be detectable, the patient will have a noticeable tumor and be demonstrating symptoms associated with the nonsense mutation. In this case **prevention** would have already failed and the administration of the compound would merely be **treatment**.

For these reasons, Applicant's arguments are not found convincing and the rejection is maintained.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaddurah-Daouk et al. (Reference cited in PTO-892) Kaddurah-Daouk et al. discloses, "a method of inhibiting growth, transformation, and/or metastasis of mammalian cells in which activity of at least one purine metabolic enzyme is elevated." (Column 2, lines 17-20) Kaddurah-Daouk et al. discloses that the class of purine metabolic enzymes includes any enzyme which participates in purine metabolism or affects the ratio of ATP

to ADP. Therefore, this class of enzymes includes those enzymes involved in DNA replication, which are elevated in all cancer cells relative to noncancerous cells due to the rapid proliferation of cancer cells. Although one embodiment of this method is directed toward cells transformed by a DNA tumor virus, Kaddurah-Daouk et al. specifically notes that mutations, such as those resulting in the loss of anti-oncogene products Rb, DCC, or p53 may mimic infection by a DNA tumor virus, leading ultimately to elevated activity of a purine metabolic enzyme. (Column 3, lines 33-37) Therefore Kaddurah-Daouk et al. discloses methods of inhibiting the growth of tumors resulting from the nonsense mutation of oncogenes such as Rb, DCC, and p53. A wide variety of drugs may be used in the method of Kaddurah-Daouk et al. For example, clitocine and its derivatives are listed as being useful for this therapeutic method. (column 27, lines 20-21) Kaddurah-Daouk et al. does not disclose as a specific embodiment of this invention a method of treating or preventing cancer resulting from a somatic mutation in DNA or RNA comprising administering an effective amount of clitocine to a patient in need thereof.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an effective amount of clitocine to a subject suffering from a cancer resulting from a somatic mutation in p53 or another oncogene which leads to elevated levels of purine metabolic enzymes. One of ordinary skill in the art would have been motivated to modify the invention of Kaddurah-Daouk et al. in this way in order to treat cancer in a patient suffering therefrom because Kaddurah-Daouk et al. lists clitocine among the various compounds useful for the treatment of cancers with an

elevated level of a purine metabolic enzyme, and discloses that a cancerous phenotype with elevated purine metabolic enzymes may be caused by loss-of-function mutations in p53 or other genes. One of ordinary skill in the art would reasonably expected success because the claimed therapeutic method is directed in part to treating cancers for which clitocine is already disclosed to be useful by Kaddurah-Daouk et al.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted November 6, 2006, with respect to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Kaddurah-Daouk does not teach methods of treating tumors resulting from the nonsense mutation of certain oncogenes, but rather is directed to inhibition of the growth of cells with elevated activity of at least one purine metabolic enzyme. However, as Applicant admits on p. 17 of the arguments, "tumors with a nonsense mutation could fall into the broad class of tumors with a 'loss of anti-oncogene products'," and, "the loss of an anti-oncogene product may ultimately lead to elevated activity of a purine metabolic enzyme." Thus Kaddurah-Daouk et al. does in fact disclose as a specific embodiment tumors in which an oncogene such as p53 has been lost. As described in MPEP § 2123, "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Thus the fact that Kaddurah-Daouk et al. is directed to the treatment of many different tumors, some of which are not associated with nonsense mutations, does not constitute a teaching away from the use of the treatment against tumors that

are associated with nonsense mutations. One of ordinary skill in the art would, from the disclosure of Kaddurah-Daouk et al., recognized that the embodiment in which the loss of anti-oncogene products Rb, DCC, or p53 produces a tumor includes several different methods by which the gene product could be lost, including epigenetic silencing, deletion mutations, frameshift mutations, and applicant's claimed embodiment of nonsense mutations.

Applicant further argues that with respect to clitocine, Kaddurah-Daouk provides only a suggestion to try, with no expectation of success. However, the language used by Kaddurah-Daouk regarding the listed compounds is, "The following drugs, which are examples of those represented by the general formula, can be used in the present method." (column 24, lines 35-37) In other words, these compounds are specifically recited as embodiments of the claimed invention and are reasonably expected to be functional embodiments of the invention. In order to adequately disclose that a compound is a function al embodiment of an invention, the disclosure does not have to explicitly list experimental data proving that each and every recited compound is functional in the disclosed invention. In the case of the ten creatine kinase inhibitors found to be non-functional, these compounds are not among the compounds recited in the list of embodiments found in columns 24-27. Therefore, contrary to Applicant's assertion, there is no reason to doubt that the recited compounds, including clitocine, are functional embodiments of the disclosed invention.

Finally, Applicant argues that Kaddurah-Daouk et al. does not disclose or suggest intravenous administration of clitocine. One of ordinary skill in the art would

recognize that intravenous administration is a very common route for systemic administration of anticancer drugs and would be able to choose an appropriate conventional method of administration, such as intravenous administration, as the proper method of administration for the claimed compound.

Thus applicant's arguments are not found to be persuasive to remove this rejection and the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 11/048659. (unpublished, cited in PTO-892) Although the

conflicting claims are not identical, they are not patentably distinct from each other because the methods of instant claims 1-19 are completely included within the limitations of claims 1-10 and 18-19 of 11/048659. Claims 1-8 of 11/048659 are drawn to a method of treating or preventing a disease responsive to modulation of premature translation termination and/or nonsense-mediated mRNA decay (including cancers caused by a somatic nonsense mutation as claimed in instant claim 1) comprising administering to a patient in need thereof an effective amount of a compound having the structure (I). (I) is a generic structure which includes the claimed compounds. Claims 9-10 of 11/048659 are drawn to methods of treating genetic diseases in the same manner. All cancers are genetic diseases.

One of ordinary skill in the art would be motivated to modify the invention in this manner in order to treat cancer in a subject suffering therefrom. One of ordinary skill in the art would reasonably expect success because the invention of instant claims 1-19 is fully included within the scope of claims 1-10 of 11/048659.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Argument: As the other rejections mentioned above are maintained, the above provisional double patenting rejection is not the sole remaining rejection in the application. Therefore the rejection is maintained.

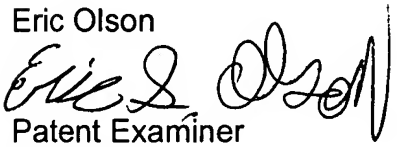
Summary

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson

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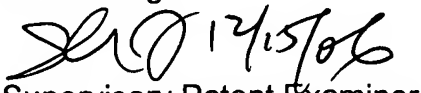
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